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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Susan L. Weston et al.

Art Unit: 1655

Serial No.: 09/228,639

Examiner: Enewold, J.

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For: Sequences

Dated: September 12, 2002

Kalow & Springut LLP
488 Madison Avenue,
19th Floor
New York, NY 10022

Assistant Commissioner for Patents
Washington, DC 20231

AMENDMENT

Sir:

This Amendment in response to the Office Action mailed March 12, 2002 in the above-referenced patent application.

Please amend the above-identified application as follows:

IN THE CLAIMS

Please cancel claims 12 and 13.

Please amend claims 1, 2, 3, 5 and 17 to read as follows:

D1

1. (Amended) A method for detecting the presence or absence of twelve mutations in the cystic fibrosis transmembrane conductor regulator (CFTR) gene, which method comprises contacting sample genomic DNA from an individual in two separate reaction vessels with allele specific primer sets, wherein:

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D1 cont'd

A) genomic DNA in the first reaction vessel is contacted with allele specific primer sets for the 1717-1 G>A, G542X, W1282X, N1303K, ΔF508(M), 3849+10kb C>T mutations, comprising SEQ. ID. No. 5, SEQ. ID. No. 7, SEQ. ID. No. 8, SEQ. ID. No. 10, SEQ. ID. No. 12, and SEQ. ID. No. 14, and

B) genomic DNA in the second reaction vessel is contacted with allele specific primer sets for the 621+1 G>T, R553X, G551D, R117H, R1162X and R334W mutations, comprising SEQ. ID. No. 16, SEQ. ID. No. 18, SEQ. ID. No. 19, SEQ. ID. No. 21, SEQ. ID. No. 23, SEQ. ID. No. 24, and SEQ. ID. No. 26,

in the presence of appropriate nucleotide-triphosphates and an agent for polymerization, such that each allele specific primer is extended only when the relevant mutation is present in the sample; and detecting the presence or absence of CFTR gene alleles by reference to the presence or absence of primer extension product(s).

D2

2. (Amended) A method according to claim 1, wherein the sample genomic DNA is amplified using amplification primers selected from the group consisting of SEQ. ID. No. 6, SEQ. ID. No. 9, SEQ. ID. No. 11, SEQ. ID. No. 13, SEQ. ID. No. 15, SEQ. ID. No.17, SEQ. ID. No. 20, SEQ. ID. No. 22, SEQ. ID. No. 25, and SEQ. ID. No. 27.

3. (Amended) A set of allele specific primers for each of the following alleles of the CFTR gene mutations: 1717-1 G>A, G542X, W1282X, N1303K, ΔF508(M), and 3849+10kb C>T, the set of allele specific primers comprising SEQ. ID. No. 5, SEQ. ID. No. 7, SEQ. ID. No. 8, SEQ. ID. No. 10, SEQ. ID. No. 12, and SEQ. ID. No. 14.

D3

5. (Amended) A set of allele specific primers for each of the following alleles of the CFTR gene mutations: 621+1 G>T, R553X, G551 D, R117H, R1162X and R334W, comprising SEQ. ID. No. 16, SEQ. ID. No. 18, SEQ. ID. No. 19, SEQ. ID. No. 21, SEQ. ID. No. 23, SEQ. ID. No. 24, and SEQ. ID. No. 26.

D4

14. (Amended) A set of primers comprising the following allele specific primer and amplification primer sequences:

TCTTGGGATT CAATAACTTT GCAACAGTCA (Seq. ID No. 5)
GAATTCCCAA ACTTTTAGAG ACATC (Seq. ID. No. 6)
TACTAMAGT GACTCTCTM TTTTCTATTT TTGGTAATTA (Seq. ID No. 7)
AGTTTGCAGA GAAAGACAAT ATAGTTCTCT (Seq. ID. No. 8)
TAATCTCTAC CAAATCTGGA TACTATACC (Seq. ID. No. 9)
TGATCACTCC ACTGTTCATA GGGATCCATC (Seq. ID. No. 10)
AATTTGAGAG AACTTGATGG TAAGTACA (Seq. ID. No. 11)
GTATCTATAT TCATCATAGG AAACACCATT (Seq. ID. No. 12)
CCAGACTTCA CTTCTAATGA TGATTATGGG (Seq. ID. No. 13)
ACATTTCCTT TCAGGGTGTC TGACTAA (Seq. ID. No. 14)
TTGTGGATCA AATTTCAGTT GACTTGTCAT C (Seq. ID. No. 15)

15. (Amended) A set of primers comprising the following allele specific primer and amplification primer sequences:

GTATCTATAT TCATCATAGG AAACCACA (Seq. ID. No. 16)
GACTTCACTT CTAATGATGA TTATGGGAGA (Seq. ID. No. 17)
TGCCATGGGG CCTGTGCAAG GAAGTATTGA (Seq. ID. No. 18)
AGCCTATGCC TAGATAAATC GCGATAGACT (Seq. ID. No. 19)
GTTTCACATA GTGTATGACC CTCTATATAC ACTCATT (Seq. ID. No. 20)
CCTATGCACTAATCAAAGGA ATCATCCTGT (Seq. ID. No. 21)
TTTGTTTATT GCTCCAAGAG AGTCATACCA (Seq. ID. No. 22)
GCTAAAGAAA TTCTTGCTCG TTGTT (Seq. ID. No. 23)
GACTGACTGACTGACTGACTCTGACTGACTTATTCACCTTGCTAAA
GAAATTCTTG CTGA (Seq. ID. No. 24)
TAAAATTGGA GCAATGTTGT TTTTGACC (Seq. ID. No. 25)
TA TTTTTATT TCAGATGCGA TCTGTGAGTT (Seq. ID. No. 26)
TTTTGCTGTG AGATCTTTGA CAGTCATTT (Seq. ID. No. 27)

D5

16. (Amended) A method according to claims 1 or 2 wherein polymerization is performed using one or more of the following control primers:

GAGCACAGTA CGAAAAACCA CCT (Seq. ID. No. 1)

AAACTTTTAC AGGGATGGAG AACG (Seq. ID. No. 2)

AGAGGATTAT CTATGCAAAT CCTTGTAACC (Seq. ID. No. 3)

TCAACTTCAC TATCAAAAGT CATCATCTAG (Seq. ID. No. 4).

17. (Amended) A diagnostic kit for detecting the presence or absence of twelve mutations, in the cystic fibrosis transmembrane conductor regulator (CFTR) gene which comprises sets of primers as claimed in anyone of claims 3, 5, 14, or 15.

Please add new claim 19 as follows:

19. (New) A set of primers as claimed in anyone of claims 3, 5, or 14 and comprising one or more of the following control primers:

GAGCACAGTA CGAAAAACCA CCT (Seq. ID. No. 1)

AAACTTTTAC AGGGATGGAG AACG (Seq. ID. No. 2)

AGAGGATTAT CTATGCAAAT CCTTGTAACC (Seq. ID. No. 3)

TCAACTTCAC TATCAAAAGT CATCATCTAG (Seq. ID. No. 4).

REMARKS

Amended Claims

Applicant has amended Claims 1, 2, 3, 5 and 17 to include specific primer sequences as set forth above in a sincere effort to more clearly and more specifically define the invention. These amendments are clearly supported in the original claims as filed and for example, at pages 4-5 of the specification. No new matter has been added. It is respectfully submitted that the amended claims presented above do in fact more clearly and specifically define the compositions and methods of the invention, and place the application in condition for allowance. Entry of the amended claims, and reconsideration of the application as amended, is respectfully requested.

Canceled claims

Claims 12 and 13 have been canceled. They have been incorporated into claims 3 or 5. Thus the pending rejections are rendered moot with regards to claims 12 and 13.

New Claim

Claim 19 is directed to specific control primers to be used in combination with the primer sets of the present invention. This new claim is supported in the specification at page 5 and the claims as originally filed. No new matter is introduced by this claim and entry is respectfully requested.

Declaration

The Examiner asserts that the declaration filed January 22, 2002 is in sufficient to overcome the rejection of Claims 1-3, 5, 12-18 based upon 103. The Examiner contends that the exhibits of the laboratory reports do not appear to identify primers by their sequence and that the exhibits are general to primers designated by mutation name, but do not give the structure of the primers.

The Examiner cites *In re Aller*, 105 USPQ 233 at 235 for showing that it is not inventive to discover the optimum or general workable range by routine experimentation. The Examiner then concludes that the present invention is mere routine experimentation and provides nothing unexpected.

Applicants respectfully disagree that only routine optimization resulted in the instant invention. Applicants have submitted declarations of Dr. Gary Brown and expert in the filed of Molecular Biology reviewing the notebooks of Susan Weston and concluding that the results she discovered were unexpected and that the references cited do not render the present invention obvious. Further, the exhibits submitted identify the primer sequences used.

In order for the present invention to be routine experimentation, the prior art must disclose the general conditions of the claimed invention requiring that the skilled artisan simply modifies the disclosed parameters to optimize expected results. None of the cited references disclose primers and/or primers sets that allow the primer sets of the claimed

invention to work in, for example, the ARMS assay. In fact the conditions were not known prior to the claimed invention that would allow the claimed primer sets to work in the ARMS assay. As shown by the exhibits and declaration, Applicants did not simply optimize a known set of primers or ARMS parameters. Applicants discovered how to design the claimed primers of the instant invention and use them simultaneously in the present invention.

The Examiner contends that "the declaration is asserting that the teaching of Schumn...is different from mutations in the CFTR gene. It is noted that the Examiner was relying upon Schumn to illustrate the multiplexing of eight pairs of primers had been successfully completed." Applicants remind the Examiner that Schumm teaches the use of simple multiplex PCR amplification of STR loci. This is a much different technique than ARMS and should not be applied as teaching ARMS multiplexing. In Schumm primers were designed to hybridize to any region flanking the site of interest. This allowed easy multiplexing of PCR reactions because any region can be selected for primer hybridization based on its ability to be multiplexed. This technique is very different from, for example, the ARMS technique. With ARMS one does not have the advantage of choosing any location outside the mutant region to design PCR primers for amplification. The artisan uses the region immediately adjacent to the mutation site. In fact the 3' terminal end of the diagnostic primer should overlap the mutation site.

Accordingly, Applicants respectfully submit that the declarations further show unexpected results and that the claimed invention was not obvious over the cited prior art.

Rejections Under 35 U.S.C. § 112

The Examiner rejects Claims 1, 2, 3, 5, and 16-18 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully disagree. Nevertheless, to expedite prosecution, Applicants have amended the claims to remove the alleged indefinite terms. Accordingly, Applicants respectfully request withdrawal of these rejections.

Rejection Under 35 U.S.C. § 102

The Examiner rejects claims 3 and 5 as being anticipated by Shuber U.S. Patent No. 5,834,181 because allele specific oligonucleotides (ASO) provided in Shuber may function as primers and are specific to certain alleles. Thus, the Examiner concludes that Shuber anticipates the claimed invention.

Applicants respectfully disagree. In order to anticipate the claimed invention, all the elements must be disclosed by the prior art reference. The present invention includes allele specific primer amplification (a primer is extended only when the relevant allele is present) as well as multiplexing up to twelve different allele specific amplification reactions simultaneously. The oligonucleotides disclosed in Shuber are for allele specific hybridization, not allele specific amplification. As such they would not function as allele specific primers for the purpose of allele specific amplification; a technique clearly taught by Applicants. With allele specific primers, the terminal 3' nucleotide is used to identify mutant or non-mutant alleles. Shuber's ASO would not function as primers in allele specific amplification because Shuber's primers are not designed to discriminate between mutant and non-mutant bases at the 3' terminal end of the oligonucleotide. Moreover, the sequences described in Columns 18 and 19 of Shuber that the Examiner refers to, bares absolutely no sequence similarity to the allele specific primers claimed by Applicants. Accordingly, since Shuber does not disclose every element of the claimed invention, then the anticipation rejection under 35 U.S.C. § 102 should be withdrawn. Applicants respectfully request withdrawal of this rejection.

First Rejection Under 35 U.S.C. § 103(a)

The Examiner rejects claim 17 under 35 U.S.C. § 103 as being obvious over Shuber in view of Ahern. The Examiner states that the ASO probes of Shuber may function as primers and are specific to certain alleles. The Examiner concedes that Shuber does not teach packaging the ASO probes of Col 18-19 in a kit. The Examiner contends that Ahern teaches the value of packaging reagent kits and combines the references with Shuber concluding that the present invention is obvious.

Applicants respectfully disagree with the Examiner. To establish obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03. The present invention includes allele specific primer amplification (a primer is extended only when the relevant allele is present) as well as multiplexing up to twelve different allele specific amplification reactions simultaneously.

The oligonucleotides disclosed by Shuber are for allele specific hybridization, not allele specific amplification. As such they would not function as allele specific primers for the purpose of allele specific amplification; a technique clearly taught by Applicants. With allele specific primers, the terminal 3' nucleotide is used to identify mutant or non-mutant alleles. Shuber's ASO probes would not function as primers in allele specific amplification because Shuber's primers are not designed to discriminate between mutant and non-mutant bases at the 3' terminal end of the oligonucleotide. Moreover, the sequences described in Columns 18 and 19 of Shuber that the Examiner refers to, bares absolutely no sequence similarity to the allele specific primers claimed by Applicants.

With regard to Ahern, this reference does not, disclose, teach or suggest the allele specific primers claimed by Applicants. Moreover, one skilled in the art would not be motivated to assemble the ASOs taught by Shuber into a kit as disclosed by Ahern for the purpose of allele specific amplification. One of ordinary skill in the art would readily recognize that the ASOs taught by Shuber would not function as allele specific primers in

an allele specific amplification reaction. Further, Applicants has submitted declarations showing unexpected results.

However, in an effort to expedite prosecution, Applicants have amended claim 17 to recite the specific allele specific primer sequences to more clearly define the instant invention.

In summary, the skilled artisan would find nothing in Shuber or Ahern alone or in combination that would disclose, teach or suggest the claimed invention or any reason for making it. Further, there is no motivation to combine the reference in such a way to get the claimed invention. Accordingly, an obviousness rejection under 35 U.S.C. § 103 is improper and Applicant requests reconsideration and withdrawal of this rejection.

Second Rejection Under 35 U.S.C. § 103(a)

Claims 1 and 2 have been rejected under 35 U.S.C. § 103(a) as being upatentable over Little et al. and Ferrie et al. and Newton in view of CFGAC.

The Examiner contends that Little discloses that the ARMS method can be used to selectively amplify multiple sites and may be useful for screening a single sample for multiple nucleotide variations, and that primers for the cystic fibrosis gene can be used. The Examiner states that Ferrie discloses the specific combination of primers taught by the present invention and Newton teaches analyzing mutations in DNA using the amplification refractory mutation system. The Examiner cites CGFAC references as disclosing the mutations used to generate the instant invention's primers. The Examiner states that it would have been *prima facie* obvious, to one of ordinary skill in the art to "have modified the teachings of Little, Ferrie and Newton in view of Estiville and CGFAC." However, it should be noted that the Examiner has not included Estiville in the rejection. Applicants will address Estiville even though it is not a formal part of the rejection.

Applicants respectfully disagree. There is no teaching or suggestion in the cited prior art that would allow on of ordinary skill in the art to combine the cited reference to obtain the diagnostic method of the instant invention using new primer sets specifically for twelve of the known CTFR mutations taught in the instant invention, or to obtain the specific primer sets themselves. Applicants are not claiming individual primers. Instead, Applicants claim sets of primers as well as a method of using sets of primers for detecting a total of twelve CFTR mutations simultaneously. Although Little discloses ARMS multiplexing of certain cystic fibrosis gene mutations using some of the same primers disclosed in the present invention, Ferrie discloses multiplex ARMS testing methods for common CFTR gene mutations, and Newton discloses analysis of mutations using the ARMS technique, there is no teaching or suggestion in Little, Ferrie or Newton, taken alone or in combination, to use the primers in the specific groupings, or sets, disclosed in the instant invention. Furthermore, although Estivill and CFGAC disclose some of the CFTR mutations corresponding to the claimed primers and their relative frequencies in various populations, the Examiner has not provided any evidence that one of ordinary skill in the art would be motivated to combine Estiville and CFGAC with Ferrie, Little and Newton to screen for CFTR mutations using the primer sets of the present invention. Instead of providing any such evidence of any disclosure or suggestion to combine the cited references, the Examiner argues that the ordinary artisan would have been able to perform routine experimentation to optimize the ARMS systems desired to suit a particular situation, based upon the cited references. Since the sequences of the CFTR gene mutations were known (Estivill and CFGAC) at the time the present invention was made, the Examiner contends that generating primers for these regions would have been obvious over Little, Ferrie and Newton which discloses the properties of the primers needed for the ARMS assay. The Examiner cites *In re Aller*, 105 USPQ 233 at 235, which states, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Applicants respectfully disagree that only routine optimization resulted in the instant invention. Assay optimization means that a particular set of parameters must function in the assay to begin with and that the skilled artisan simply modifies the

disclosed parameters to optimize the results of the assay. Indeed *In re Aller* states that the general conditions of a claim must be disclosed. None of Little, Ferrie, Newton, Estiville or CFGAC defines or discloses conditions that would allow the primer sets of the instant invention, comprising twelve different primers, to function in the ARMS assay and provide meaningful results. In fact the conditions were not known prior to the instant invention that would allow the primer sets claimed to function in the ARMS assay. Applicants did not simply optimize a known set of parameters. Applicants discovered how to design the primers and get them to work together simultaneously in primer sets.

There is simply no teaching or suggestion in any of the references, alone or in combination, of the specific primers of the present invention, i.e., having the lengths, and combinations taught by the present invention and methods of using these primers in multiplex analysis with unexpected results demonstrated in the specification (see Examples 1,2, and Table 2).

The Examiner's rejection is founded on an impermissible "obvious to try" standard, i.e., to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gives only general guidance as to how to achieve the claimed invention. Further, the rejection cannot be founded upon a "routine optimization" standard when the general conditions needed for an assay to function properly were not disclosed in the art. It would have been impossible to optimize a set of assay parameters that did not exist in the first place.

In the present case, the particular sets of primers disclosed are unique and non-obvious, and none of Little, Ferrie or Newton discloses the specific combination of primers taught by the present invention. Ferrie, Little and Newton may provide general guidance as to how to design multiplex ARMS tests, but there is no motivation to combine Little, Ferrie and Newton's disclosures with those of Estivill and CGFAC references, which teach CFTR mutations in general populations, to obtain the particular sets of primers claimed in the present invention. Further, Applicants note that the primers

and conditions disclosed were the surprising or unexpected results of research by the inventors. Monthly reports have been submitted along with Declarations showing the unexpected results.

However, in an effort to expedite prosecution, Applicants have amended claims 1 and 2 to recite the specific allele specific primer sequences to more clearly define the instant invention. The claims as amended are not "obvious or unpatentable over Little, Ferrie, Newton Estivill or CFGAC and Applicants respectfully request that the rejection of claims 1 and 2 under 35 U.S.C. § 103(a) be withdrawn.

Third Rejection Under 35 U.S.C. § 103(a)

Claims 3, 5 and 17 have been rejected under 35 U.S.C. § 103(a) as being upatentable over Little et al. and Ferrie et al. in view of Estivill and CFGAC.

The Examiner contends that Little discloses numerous primers for ARMS analysis and that primers SEQ ID NO. 12, 16, 17, 18 are identical to the Little primers 1878, 1880, 1879 and 2072 respectively and that Little teaches placing the primers into a kit. The Examiner cites Newton as teaching the analysis of mutations in DNA using the amplification refractory mutation system. The Examiner cited further CGFAC references as disclosing the mutations used to generate the instant invention's primers. The Examiner states that it would have been *prima facie* obvious, to one of ordinary skill in the art to "have modified the teachings of Little and Newton in view of CGFAC." Applicants will address Newton even though it is not a formal part of the rejection.

Applicants respectfully disagree. As stated above, there is no teaching or suggestion in the cited prior art that would allow on of ordinary skill in the art to combine the cited reference to obtain the diagnostic method of the instant invention using new primer sets specifically for twelve of the known CTFR mutations taught in the instant invention, or to obtain the specific primer sets themselves. Applicants are not claiming

individual primers. Instead, Applicants claim sets of primers as well as a method of using sets of primers for detecting a total of twelve CFTR mutations simultaneously. Although Little discloses ARMS multiplexing of certain cystic fibrosis gene mutations using some of the same primers disclosed in the present invention, Ferrie discloses multiplex ARMS testing methods for common CFTR gene mutations, and Newton discloses analysis of mutations using the ARMS technique, there is no teaching or suggestion in Little, Ferrie or Newton, taken alone or in combination, to use the primers in the specific groupings, or sets, disclosed in the instant invention. Furthermore, although Estivill and CFGAC disclose some of the CFTR mutations corresponding to the claimed primers and their relative frequencies in various populations, the Examiner has not provided any evidence that one of ordinary skill in the art would be motivated to combine Estivill and CFGAC with Ferrie, Little and Newton to screen for CFTR mutations using the primer sets of the present invention. Instead of providing any such evidence of any disclosure or suggestion to combine the cited references, the Examiner argues that the ordinary artisan would have been able to perform routine experimentation to optimize the ARMS systems desired to suit a particular situation, based upon the cited references. Since the sequences of the CFTR gene mutations were known (Estivill and CFGAC) at the time the present invention was made, the Examiner contends that generating primers for these regions would have been obvious over Little, Ferrie and Newton which discloses the properties of the primers needed for the ARMS assay.

In the claimed invention, the particular sets of primers disclosed are unique and non-obvious, and none of Little, Ferrie or Newton discloses the specific combination of primers taught by the present invention. Ferrie, Little and Newton may provide general guidance as to how to design multiplex ARMS tests, but there is no motivation to combine Little, Ferrie and Newton's disclosures with those of Estivill and CGFAC references, which teach CFTR mutations in general populations, to obtain the particular sets of primers claimed in the present invention. Furthermore, Applicants did not simply optimize a known set of ARMS assay primers and conditions. Assay optimization means that a particular set of parameters must function in the assay to begin with and that the

skilled artisan simply modifies the disclosed parameters to optimize the results of the assay. Indeed *In re Aller* states that the general conditions of a claim must be disclosed. None of Little, Ferrie, Newton, Estiville or CFGAC defines or discloses conditions that would allow the primer sets of the instant invention, comprising twelve different primers, to function in the ARMS assay and that provide meaningful results. In fact the conditions were not known prior to the instant invention that would allow the primer sets claimed to function in the ARMS assay. Applicants did not simply optimize a known set of parameters. Applicants discovered how to design the primers of the instant invention and allow them to function together simultaneously in primer sets.

There is simply no teaching or suggestion in any of the references, alone or in combination, of the specific primers of the present invention, i.e., having the lengths, and combinations taught by the present invention and methods of using these primers in multiplex analysis with unexpected results demonstrated in the specification (see Examples 1,2, and Table 2). Further, Applicants note that the primers sets disclosed were the surprising or unexpected results of research by the inventors. Monthly reports have been submitted along with Declarations showing the unexpected results.

However, in an effort to expedite prosecution, Applicants have amended claims 3, 5 and 17 to recite the specific allele specific primer sequences to more clearly define the instant invention. The claims as amended are not "obvious or unpatentable over Little, Ferrie, Newton, Estivill or CFGAC and applicants respectfully request that the rejection of claims 3, 5 and 17 under 35 U.S.C. § 103(a) be withdrawn.

Fourth Rejection Under 35 U.S.C. § 103(a)

Claims 12, 13, 14, 15 and 17 have been rejected under 35 U.S.C. § 103(a) as being upatentable over Little et al. and Ferrie et al. in view of Estivill and CFGAC.

The Examiner contends that Little discloses numerous primers for ARMS analysis and that primers SEQ ID NO. 12, 16, 17, 18 are identical to the Little primers 1878,

1880, 1879 and 2072 respectively and that Little teaches placing the primers into a kit. The Examiner states that Ferrie discloses the specific combination of primers taught by the present invention and Newton teaches analyzing mutations in DNA using the amplification refractory mutation system. The Examiner cites Newton as teaching the analysis of mutations in DNA using the amplification refractory mutation system. The Examiner cites further Estivill and CGFAC references as disclosing the relative frequencies of the mutations in numerous populations. The Examiner states " Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC. The Examiner states further that ordinary artisan would have been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Applicants will address Newton even though it is not a formal part of the rejection.

Applicants respectfully disagree. As stated above, there is no teaching or suggestion in the cited prior art that would allow one of ordinary skill in the art to combine the cited reference to obtain the diagnostic method of the instant invention using new primer sets specifically for twelve of the known CTFR mutations taught in the instant invention, or to obtain the specific primer sets themselves. Applicants are not claiming individual primers. Instead, Applicants claim sets of primers as well as a method of using sets of primers for detecting a total of twelve CFTR mutations simultaneously. Although Little discloses ARMS multiplexing of certain cystic fibrosis gene mutations using some of the same primers disclosed in the present invention, Ferrie discloses multiplex ARMS testing methods for common CFTR gene mutations, and Newton discloses analysis of mutations using the ARMS technique, there is no teaching or suggestion in Little, Ferrie or Newton, taken alone or in combination, to use the primers in the specific groupings, or sets, disclosed in the instant invention. Furthermore, although Estivill and CFGAC disclose the CFTR mutations corresponding to the claimed

primers and their relative frequencies in various populations, the Examiner has not provided any evidence that one of ordinary skill in the art would be motivated to combine Estivill and CFGAC with Ferrie, Little and Newton to screen for CFTR mutations using the primer sets of the present invention. Instead of providing any such evidence of any disclosure or suggestion to combine the cited references, the Examiner argues that the ordinary artisan would have been able to perform routine experimentation to optimize the ARMS systems desired to suit a particular situation, based upon the cited references. Since the sequences of the CFTR gene mutations were known (Estivill and CFGAC) at the time the present invention was made, the Examiner contends that generating primers for these regions would have been obvious over Little, Ferrie and Newton which discloses the properties of the primers needed for the ARMS assay.

In the presently claimed invention, the particular sets of primers disclosed are unique and non-obvious, and none of Little, Ferrie or Newton discloses the specific combination of primers taught by the present invention. Ferrie, Little and Newton may provide general guidance as to how to design multiplex ARMS tests, but there is no motivation to combine Little, Ferrie and Newton's disclosures with those of Estivill and CGFAC references, which teach CFTR mutations in general populations, to obtain the particular sets of primers claimed in the present invention. The Examiner states "...the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC. Applicants ask where in Little, Ferrie, Estivill or the CFAC is the motivation found to combine these references to yield the specific combination of primers taught by the present invention or to invent the means necessary to use the primers taught by the present invention in primers sets.

Furthermore, Applicants did not simply optimize a known set of ARMS assay primers and conditions. Assay optimization means that a particular set of parameters

must function in the assay to begin with and that the skilled artisan simply modifies the disclosed parameters to optimize the results of the assay. Indeed, *In re Aller* states that the general conditions of a claim must be disclosed. None of Little, Ferrie, Newton, Estiville or CFGAC defines or discloses conditions that would allow the primer sets of the instant invention, comprising twelve different primers, to function in the ARMS assay and provide meaningful results. In fact the conditions were not known prior to the instant invention that would allow the primer sets claimed to function in the ARMS assay. Applicants did not simply optimize a known set of parameters. Applicants discovered how to design the primers of the instant invention and get them to work together simultaneously in primer sets.

The Examiner goes on to state "the ordinary artisan would have optimized primer selection to obtain results for the ARMS reaction, based upon the teachings of optimization by Ferrie. The Examiner cited *In re Deuel* 34 USPQ 2d (Fed.Cir 1995) stating that "a primary facie case of obviousness is based upon structural similarity...and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." The Examiner then states that "the claimed primers simply represent functional equivalents of the primers taught by Little, Ferrie and Newton in view of the known CFTR gene, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties..."

Applicants respectfully disagree. Primers are not homologs of genes. Instead, a primer is an extendable chain of nucleic acid, where an additional nucleic acid can be added to the chain using a polymerase. Homologs are not used in the biological arts to compare different classes of nucleic acids such as primers and genes.

In the present case the compounds previously disclosed, such as the CFTR mutations and certain primers to these mutations, do not suggest the design of appropriate diagnostic primers or sets of primers. Knowledge of a template sequence does not render the design of such primers obvious. There is simply no disclosure or suggestion in any of

the references, alone or in combination, of the specific primers of the present invention, i.e., having the lengths and combinations taught by the present invention and methods of using these primers in multiplex analysis with unexpectedly results demonstrated in the specification (see Examples 1,2, and Table 2).

The rejection as obvious over the prior art cannot be founded on an impermissible "obvious to try" standard, i.e., to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gives only general guidance as to how to achieve the claimed invention. For an invention to be obvious over the prior art, the prior art must teach or suggest the invention. The Examiner is using an impermissible hindsight reconstruction of the claimed invention based upon a general motivation to search for primers. Further, the rejection cannot be founded upon a "routine optimization" standard when the general conditions needed for an assay to function properly were not disclosed in the art. It would have been impossible to optimize a set of assay parameters that did not exist in the first place.

Applicants maintain that the claimed sets of primers unexpectedly work together in the multiplex ARMS reaction to detect the presence or absence of twelve known CFTR mutations. These sets of primers are able, unexpectedly, to detect the specific mutations reliably and robustly, as shown in the specification, particularly in Table 2 and in Examples 1 and 2.

Further, Applicants note that the primers disclosed were the surprising or unexpected results of research by the inventors. Monthly reports have been submitted along with Declarations showing the unexpected results.

In view of the above amendments, the above discussion of the claims, and the Declarations, Applicants maintain that the cited references, alone or in combination, do not teach or suggest the present invention. Accordingly, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103, be reconsidered and withdrawn.

CONCLUSION

All of the stated grounds of the rejections have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that the present application is in condition for Allowance.

If a telephone conference would be of assistance in furthering the prosecution of the application, Applicants' undersigned attorney requests that he be contacted at the telephone number provides below.

If additional fees are deemed necessary for the filing of this Amendment, authorization is hereby given to charge any such fees to Deposit Account No. 11-0171. Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

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